

WHAT IS CLAIMED IS:

1. A method for treating a human having a pathology mediated by tumor necrosis factor, TNF, comprising administering to said human a TNF inhibiting effective amount of an anti-TNF chimeric antibody.

2. A method according to claim 1, wherein said anti-TNF chimeric antibody comprises a non-human variable region and a human constant region, or a portion thereof.

3. A method according to claim 2, further comprises a pharmaceutical carrier.

4. A method according to claim 3, wherein said anti-TNF antibody comprises an immunoglobulin variable region, said region capable of binding an epitope specific for human TNF.

5. A method according to claim 3, wherein said anti-TNF antibody is a chimeric immunoglobulin chain further comprising at least part of a human immunoglobulin constant region.

6. A method according to claim 4, wherein said immunoglobulin variable region is of murine origin.

7. A method according to claim 4, wherein said anti-TNF antibody is a chimeric immunoglobulin chain capable of competitively binding to an epitope specific for human TNF $\alpha$  with a monoclonal antibody selected from A2 and cA2.

8. A method according to claim 7, wherein said anti-TNF antibody is selected from A2 and cA2.

9. A method according to claim 8, wherein said antibody is cA2.

10. A method according to claim 8, wherein said antibody is A2.

11. A method for treating a human having a pathology mediated by tumor necrosis factor, TNF, comprising administering to said human a TNF inhibiting effective amount of an anti-tissue necrosis factor, TNF, peptide.

12. A method according to claim 11, wherein said anti-TNF peptide is selected from the group consisting of a portion of an anti-TNF antibody variable region, a fragment

of a TNF receptor and an anti-TNF structural analog, said anti-TNF peptide capable of binding human TNF.

13. A method according to claim 12, wherein said anti-TNF peptide is a portion of an antibody variable region.

14. A method according to claim 12, wherein said anti-TNF peptide is a fragment of a TNF receptor.

15. A method according to claim 12, wherein said structural analog corresponds to a portion of the receptor fragment or the antibody such that the analog is capable of binding a TNF with neutralizing activity.

16. A method according to claim 12, wherein said peptide comprises a TNF binding immunoreceptor molecule, said immunoreceptor molecule, comprising at least a portion of an immunoglobulin heavy chain CH<sub>1</sub> region, at least a portion of a hinge region and at least one immunoglobulin light chain constant region wherein at least one immunoglobulin chain is covalently linked to a non-immunoglobulin molecule capable of binding to at least one of TNF $\alpha$  and TNF $\beta$ .

17. A method according to claim 16, wherein said immunoreceptor molecule further comprises at least a portion of an immunoglobulin heavy chain CH<sub>1</sub> region, at least a portion of a hinge region and at least one immunoglobulin light chain constant region.

18. A method according to claim 17, wherein said immunoreceptor molecule further comprises at least a portion of CH<sub>3</sub> or CH<sub>2</sub>.

19. A method according to claim 16, wherein said at least one non-immunoglobulin molecule is covalently linked to the N-terminus of at least one CH<sub>1</sub> region.

20. A method according to claim 16, wherein said at least one non-immunoglobulin molecule is covalently linked to an interior section of at least one heavy chain region.

21. A method according to claim 17, wherein said the heavy chain further comprises a variable region capable of binding to a second target molecule.

22. A method according to claim 17, wherein said

the heavy chain is an IgG class heavy chain.

23. A method according to claim 16, wherein said the non-immunoglobulin molecule comprises at least a portion of p55.

24. A method according to claim 23, wherein the non-immunoglobulin molecule comprises sequences 2-159 of p55.

25. A method according to claim 24, wherein the non-immunoglobulin molecule comprises sequences 1-235 of p75.

26. A method according to claim 25, wherein said non-immunoglobulin molecule comprises sequences 1-182 of p75.

27. A method according to claim 26, wherein the non-immunoglobulin molecule comprises sequences 1-178 of p75.

28. A method according to claim 17, wherein the heavy chain further comprises at least about 8 amino acids of a J region.

29. A method according to claim 23, said molecule having two non-immunoglobulin molecules, each comprising at least a portion of p55.

30. A method according to claim 23, said molecule having four non-immunoglobulin molecules, each comprising at least a portion of p55.

31. A method according to claim 24, said molecule having two non-immunoglobulin molecules, each comprising at least a portion of p75.

32. A method according to claim 24, said molecule having four non-immunoglobulin molecules, each comprising at least a portion of p75.

33. A method according to claim 16, wherein said immunoreceptor molecule is capable of binding with high affinity to a neutralizing epitope of human TNF $\alpha$  *in vivo*.

34. A method according to claim 33, wherein the binding affinity is at least about  $1.6 \times 10^{10}$  1/mole.

35. A method according to claim 17, wherein said immunoreceptor molecule is capable of neutralizing TNF wherein a concentration of less than about 130 pM is capable of neutralizing about 39.2 pM human TNF $\alpha$ .

36. A method according to claim 15, wherein said

structural analog corresponds to at least a portion of a p75 or p55 extracellular region capable of binding to at least one of TNF $\alpha$  and TNF $\beta$ .

5 37. A method according to claim 36, wherein the extracellular region comprises sequences 1-235 of p75.

10 38. A method for treating a vertebrate suspected of having a condition associated with elevated levels of TNF in a body fluid, comprising administering to the vertebrate a TNF inhibiting effective amount of an anti-TNF compound according to a method of claim 1.

39. A method according to claim 37, wherein said extracellular region comprises sequences 1-182 of p75.

15 40. A method according to claim 2, wherein said extracellular region comprises sequences 2-159 of p55.

41. A method according to claim 15, wherein said structural analog further comprises at least a portion at an immunoglobulin heavy chain CH region, at least a portion of a huge region and at least one immunoglobulin light chain constant region.

20 *sub* 42. A method according to claim 1, wherein said pathology is selected from the group consisting of a chronic inflammatory pathology, an autoimmune disease, an infection, a neurodegenerative disease, and a malignant pathology.

25 43. A method according to claim 42, wherein said pathology is an inflammatory pathology.

44. A method according to claim 43, wherein said inflammatory pathology is selected from the group consisting of a chronic inflammatory pathology and a vascular inflammatory pathology.

30 45. A method according to claim 44, wherein said inflammatory pathology is a chronic inflammatory pathology.

35 46. A method according to claim 45, wherein said chronic inflammatory pathology is selected from the group consisting of sarcoidosis, chronic inflammatory bowel disease, ulcerative colitis and Crohn's disease.

47. A method according to claim 46, wherein said pathology is Crohn's disease.

48. A method according to claim 46, wherein said pathology is ulcerative colitis.

49. A method according to claim 43, wherein said inflammatory pathology is a vascular inflammatory pathology.

50. A method according to claim 43, wherein said vascular inflammatory pathology is selected from the group consisting of disseminated intravascular coagulation, atherosclerosis and Kawasaki's pathology.

51. A method according to claim 42, wherein said pathology is an autoimmune disease.

52. A method according to claim 51, wherein said autoimmune disease is selected from the group consisting of pemphigus, Grave's disease, myasthenia gravis, insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, scleroderma, polymyositis, and pernicious anemia, systemic lupus erythematosus, SLE, rheumatoid arthritis, thyroiditis, graft versus host disease, scleroderma, and diabetes mellitus.

53. A method according to claim 52, wherein said autoimmune disease is rheumatoid arthritis.

54. A method according to claim 52, wherein said autoimmune disease is SLE.

55. A method according to claim 42, wherein said pathology is an infection.

56. A method according to claim 55, wherein said infection is selected from the group consisting of sepsis syndrome, cachexia, a bacterial infection, circulatory collapse and shock resulting from a bacterial infection, a viral infection, and a fungal infection.

57. A method according to claim 56, wherein said infection is a viral infection.

58. A method according to claim 57, wherein said viral infection is an HIV infection.

59. A method according to claim 57, wherein said viral infection is AIDS.

60. A method according to claim 42, wherein said pathology is a neurodegenerative disease.

61. A method according to claim 60, wherein said neurodegenerative disease is selected from the group consisting of AIDS dementia complex, a demyelinating disease, multiple sclerosis, acute transverse myelitis, an  
5 extrapyramidal disorder, a cerebellar disorder, a lesion of the corticospinal system, a disorder of the basal ganglia, a cerebellar disorder, a hyperkinetic movement disorder, Huntington's Chorea, senile chorea, a drug-induced movement disorder, a hypokinetic movement disorder, Parkinson's  
10 disease, progressive supranucleo palsy, a structural lesion of the cerebellum, a spinocerebellar degeneration, spinal ataxia, Friedreich's ataxia, a cerebellar cortical degeneration, a multiple systems degeneration, a systemic disorder, Refsum's disease, abetalipoproteinemia, ataxia  
15 telangiectasia, a mitochondrial multi-system disorder, a demyelinating core disorder, acute transverse myelitis, a disorder of the motor unit, a neurogenic muscular atrophy, anterior horn cell degeneration, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal  
20 muscular atrophy, Alzheimer's disease, Down's Syndrome, a diffuse Lewy body disease, senile dementia of Lewy body type, Wernicke-Korsakoff syndrome, chronic alcoholism, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, Hallerorden-Spatz disease and dementia pugilistica.

25 62. A method according to claim 61, wherein said neurodegenerative disease is multiple sclerosis.

63. A method according to claim 61, wherein said neurodegenerative disease is AIDS dementia complex.

30 64. A method according to claim 61, wherein said neurodegenerative disease is multiple sclerosis.

65. A method according to claim 61, wherein said neurodegenerative disease is Alzheimer's disease.

66. A method according to claim 42, wherein said pathology is a malignant pathology.

35 67. A method according to claim 60, wherein said malignant pathology is selected from the group consisting of a tumor, a lymphoma and a leukemia.

67. A method according to claim 60, wherein said malignant pathology is selected from the group consisting of a tumor, a lymphoma and a leukemia.

5 68. A method according to claim 60, wherein said malignant pathology is selected from the group consisting of a tumor, a lymphoma and a leukemia.

69. A method according to claim 68, wherein said pathology is a tumor.

10 70. A method according to claim 69, wherein said tumor is a TNF secreting tumor.

71. A method according to claim 70, wherein said TNF secreting tumor secretes TNF $\alpha$ .

72. A method according to claim 70, wherein said TNF secreting tumor secretes TNF $\beta$ .

15 73. A method according to claim 68, wherein said pathology is a lymphoma.

20 74. A method according to claim 73, wherein said lymphoma is selected from the group consisting of acute lymphoma, chronic myelocytic lymphoma, chronic lymphocytic and/or myelodysplastic syndrome

75. A method according to claim 68, wherein said pathology is a leukemia.

25 76. A method according to claim 14, wherein said fragment comprises at least a portion of p55.

77. A method according to claim 76, wherein said fragment comprises sequences 2-159 of p55.

78. A method according to claim 14, wherein said fragment comprises at least a portion of p75.

30 79. A method according to claim 78, wherein said fragment comprises sequences 1-235 of p75.

80. A method according to claim 79, wherein said fragment comprises sequences 1-182 of p75.

81. A method according to claim 80, wherein said fragment comprises sequences 1-178 of p75.

35 82. A method according to claim 11, wherein said pathology is selected from the group consisting of a chronic inflammatory pathology, an autoimmune disease, an infection,

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a neurodegenerative disease, and a malignant pathology.

83. A method according to claim 82, wherein said pathology is an inflammatory pathology.

5 84. A method according to claim 83, wherein said inflammatory pathology is selected from the group consisting of a chronic inflammatory pathology and a vascular inflammatory pathology.

85. A method according to claim 84, wherein said inflammatory pathology is a chronic inflammatory pathology.

10 86. A method according to claim 85, wherein said chronic inflammatory pathology is selected from the group consisting of sarcoidosis, chronic inflammatory bowel disease, ulcerative colitis and Crohn's pathology.

15 87. A method according to claim 86, wherein said pathology is Crohn's disease.

88. A method according to claim 86, wherein said pathology is ulcerative colitis.

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20 89. A method according to claim 83, wherein said autoimmune disease is a vascular inflammatory pathology.

90. A method according to claim 89, wherein said vascular inflammatory pathology is selected from the group consisting of disseminated intravascular coagulation, atherosclerosis and Kawasaki's pathology.

25 91. A method according to claim 82, wherein said pathology is an autoimmune disease.

30 92. A method according to claim 43, wherein said autoimmune disease is selected from the group consisting of pemphigus, Grave's disease, myasthenia gravis, insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, scleroderma, polymyositis, and pernicious anemia, systemic lupus erythematosus, SLE, rheumatoid arthritis, thyroidosis, graft versus host disease, scleroderma, and diabetes mellitus.

35 93. A method according to claim 92, wherein said autoimmune disease is rheumatoid arthritis.

94. A method according to claim 92, wherein said autoimmune disease is SLE.



95. A method according to claim 82, wherein said pathology is an infection.

96. A method according to claim 95, wherein said infection is selected from the group consisting of sepsis syndrome, cachexia, a bacterial infection, circulatory collapse and shock resulting from a bacterial infection, a viral infection, and a fungal infection.

97. A method according to claim 96, wherein said infection is a viral infection.

98. A method according to claim 97, wherein said viral infection is an HIV infection.

99. A method according to claim 97, wherein said viral infection is AIDS.

100. A method according to claim 82, wherein said pathology is a neurodegenerative disease.

101. A method according to claim 99, wherein said neurodegenerative disease is selected from the group consisting of AIDS dementia complex, a demyelinating disease, multiple sclerosis, acute transverse myelitis, an extrapyramidal disorder, a cerebellar disorder, a lesion of the corticospinal system, a disorder of the basal ganglia, a cerebellar disorder, a hyperkinetic movement disorder, Huntington's Chorea, senile chorea, a drug-induced movement disorder, a hypokinetic movement disorder, Parkinson's disease, progressive supranucleo palsy, a structural lesion of the cerebellum, a spinocerebellar degeneration, spinal ataxia, Friedreich's ataxia, a cerebellar cortical degeneration, a multiple systems degeneration, a systemic disorder, Refsum's disease, abetalipoproteinemia, ataxia telangiectasia, a mitochondrial multi-system disorder, a demyelinating core disorder, acute transverse myelitis, a disorder of the motor unit, a neurogenic muscular atrophy, anterior horn cell degeneration, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Alzheimer's disease, Down's Syndrome, a diffuse Lewy body disease, senile dementia of Lewy body type, Wernicke-Korsakoff syndrome, chronic alcoholism, Creutzfeldt-

Jakob disease, subacute sclerosing panencephalitis,  
Hallerrorden-Spatz disease and dementia pugilistica.

102. A method according to claim 101, wherein said  
neurodegenerative disease is multiple sclerosis.

103. A method according to claim 101, wherein said  
neurodegenerative disease is AIDS dementia complex.

104. A method according to claim 101, wherein said  
neurodegenerative disease is multiple sclerosis.

105. A method according to claim 101, wherein said  
neurodegenerative disease is Alzheimer's disease.

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Add H<sup>2</sup>